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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/371,347	08/10/1999	ROY A. GRAVEL	50004/003003	9130

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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	28

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/371,347	GRAVEL ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 36-53* is/are pending in the application.

4a) Of the above claim(s) *48 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,36-47 and 50-53* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-5, 36-53 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's species election without traverse of SEQ ID NO: 25 in Paper No. 27, filed on 5/27/2003 is acknowledged.

As indicated in previous Office Action Paper No. 25, mailed on 12/19/2002, claims 47-50 are generic. Upon allowance of a generic claim, Applicants are entitled to consideration of claims to additional species which are written in dependent form or otherwise include the limitations of an allowed generic claim as provided by 37 CFR 1.141 and MPEP 809.02(a).

Claims 48-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/071,622 filed on 1/16/1998.

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/232,028 filed on 1/15/1999.

Drawings

3. According to PTO records, the drawings have been reviewed and were objected under 37 CFR 1.84 or 1.152. See Notice of Draftsperson's Patent Drawing Review submitted with Paper No. 11 on 3/5/2001. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

4. Claim 5 is objected to because of the following informalities: for clarity, it is suggested that the term "at least 50% of at least 60 contiguous nucleotides" be replaced with "at least 30 contiguous nucleotides". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 4-5, 35, 39-47, 50-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 4 (claims 5, 35 and 53 dependent thereof) is indefinite in the recitation of "nucleic acid that hybridizes....to a sequence.." for the following reasons. As known in the art, a sequence is a graphical representation of the order in which nucleotides/amino acids are arranged in a molecule. Since hybridization occurs between molecules, it is unclear as to how a sequence can hybridize to a nucleic acid. For examination purposes, it will be assumed that the term reads "nucleic acid that hybridizes... to the polynucleotides of SEQ ID NO: 1 or 41. Correction is required.

8. Claim 4 (claims 5, 35 and 53 dependent thereof) is indefinite in the recitation of "nucleic acid comprises a region complementary to a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism" for the following reasons. As indicated in the specification, a mutation or a polymorphism can be a single nucleotide substitution or a deletion of a limited number of nucleotides, such as those recited in claim 35. Therefore, in the absence of an additional structural limitation defining the area comprising the naturally-occurring mutation/polymorphism which is specific for a mammalian methionine synthase reductase polynucleotide, and/or in the absence of a limitation defining which specific mutations or polymorphisms are encompassed by the claims, it is unclear as to whether any polynucleotide which has any nucleotide in any position (polymorphism) or lacks any nucleotide fragment (deletion) and hybridizes to the polynucleotides of SEQ ID NO: 1 or 41 is encompassed by the claim. For examination purposes, it will be assumed that the claim encompasses any polynucleotide which hybridizes under the recited conditions to the polynucleotide of SEQ ID NO: 1 or 41 and wherein said polynucleotide comprises a region which is completely complementary to a fragment of a mammalian methionine synthase reductase nucleic acid

wherein said fragment comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism. Correction is required.

9. Claims 39 and 41 (claims 40 and 42-44, 51-53 dependent thereof) are indefinite in the recitation of "nucleic acid of claim 36 comprising a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism" or "nucleic acid comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism" for the following reasons. Since there is no structural limitation in regard to the naturally-occurring mammalian methionine synthase reductase mutation/polymorphism and/or which mutations or polymorphisms are included (i.e. specific substitutions, insertions or deletions), it is unclear as to how the terms further limit the claims. See discussion above in regard to claim 4. For examination purposes, it will be assumed that the claim is directed to any polynucleotide which is at least 50% sequence identical to the polynucleotide of SEQ ID NO: 1 over the entire length of SEQ ID NO: 1 and comprise a fragment of any mammalian methionine synthase reductase nucleic acid, wherein said fragment comprises a naturally-occurring mammalian synthase reductase mutation or polymorphism. Correction is required.

10. Claims 35, 40 and 44 are indefinite in the recitation of "the nucleic acid of claim 4 (39 or 41) wherein said mutation or polymorphism is an alteration relative to SEQ ID NO: 1 selected from the group consisting of: a) the alteration of guanine to adenine at nucleotide position 66....., b)...at nucleotide position 110, c)....." for the following reasons. The alterations at the positions recited refer to SEQ ID NO: 1 and there is no limitation in the claims in regard to polynucleotide size, therefore, it is unclear as to how these positions correlate with a polynucleotide of any size which hybridizes under the recited conditions to the polynucleotides

of SEQ ID NO: 1 or 41, or how they correlate with a polynucleotide of any size which is at least 50% sequence identical to the polynucleotide of SEQ ID NO: 1. For examination purposes, claim 35 will be interpreted as being directed to a polynucleotide which hybridizes to the polynucleotide of SEQ ID NO: 1 or 41, wherein said polynucleotide comprises the complete complement of (1) nucleotides 50-70 of SEQ ID NO: 1 except that the guanine base at position 66 is changed to adenine, (2) nucleotides 100-120 of SEQ ID NO: 1 except that guanine base at position 110 is changed to adenine, (3) nucleotides 1600-1700 of SEQ ID NO: 1 except that bases 1675-1678 have been deleted, (4) nucleotides 1700-1800 of SEQ ID NO: 1 except that bases 1726-1728 have been deleted. Claims 40 and 44 will be interpreted as being directed to a 50% sequence homolog of the polynucleotide of SEQ ID NO: 1 wherein said polynucleotide comprises (1), (2), (3) or (4) as described above. Correction is required.

11. Claims 41-43 (claims 44-47, 50-53 dependent thereof) are indefinite in the recitation of "sequence that has at least #% sequence identity to the corresponding region of SEQ ID NO: 1" since one cannot determine which corresponding region of SEQ ID NO: 1 is being referred to. For examination purposes, the term will be interpreted as "sequence that has at least #% sequence identity to the polynucleotide of SEQ ID NO: 1". Correction is required.

12. Claims 45-46 are indefinite in the recitation of "polypeptide having at least 20-30% of the ability to catalyze.....as the methionine synthase reductase polypeptide of SEQ ID NO: 2" as it unclear and confusing. For examination purposes, the term will be interpreted as "polypeptide having at least 20-30% of the ability to catalyze...as that of the methionine synthase reductase polypeptide of SEQ ID NO: 2". Correction is required.

13. Claim 47 remains rejected as indefinite due to the recitation of "consensus binding site for one or more cofactors" as it is unclear which are the residues of the consensus binding site encompassed by the claims. Applicants argue that one of skill in the art would readily recognize a consensus binding site for FAD, FMN, and/or NADPH cofactors and submit evidence in support of this assertion in a Declaration by Inventor Gravel, a reference in Appendix A by Wang et al. (Proc. Natl. Acad. Sci. USA 94:8411-8416, 1997), and a sequence alignment of CPR family members taken from the Wang et al. reference in Appendix B. Neither the declaration nor the references submitted have been found persuasive to overcome the rejection in view of the significant sequence variation within the FAD, FMN and NADPH consensus binding sites shown in Appendix B. As such, it is unclear as to how one can reasonably establish which are the consensus binding sites encompassed by the claim.

14. Claim 52 is indefinite in the recitation of "administration of said nucleic leads to a decrease..." as it is unclear what the meaning of the term is. For examination purposes, it will be assumed that the term reads "administration of said nucleic acid leads to a decrease...". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-2, 4-5, 35-47, 50-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

17. This rejection has been applied to claims 1-2, 4-5, 35-47 by the previous Examiner of record in Paper No.11 mailed on 11 3/5/2001 and Paper No. 14, mailed on 11/16/2001. It is now applied to newly added claims 50-53 for the reasons of record and for the reasons set forth below.

18. Applicants argue that the specification teaches several full-length mammalian methionine synthase reductases including SEQ ID NO: 1, 41, 43, 45 and 47. Furthermore, Applicants submit that the specification teaches other structural characteristics such as consensus binding sites for FAD, FMN, and NADPH and functional characteristics such as the ability of a mammalian methionine synthase reductase to generate co(iii)alamin-CH3 from the reductive methylation of cob(II)alamin or to increase methionine synthase activity by maintaining the cobalamin cofactor of methionine synthase in an active state. Applicants also argue that one of skill in the art would expect a high degree of conservation among mammalian methionine synthase reductases, therefore there is a great level of predictability inherent in the practice of the invention. Applicants submit that in addition to the teachings described, the specification teaches enzymatic assays. Furthermore, Applicants submit that the specification structurally characterizes the polynucleotides of SEQ ID NO: 43, 45 and 47, which hybridize to the polynucleotides of 1 and 41, by providing their sequences, and that the specification also discloses many primers (Table 1), antisense nucleic acids, and numerous assays which can be used to further characterize such nucleic acids.

19. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection in regard to claims 1-2, 4-5, 35-47 or to avoid the rejection of newly added claims 50-53. Claims 1-2 are directed to a genus of mammalian or human methionine synthase reductases having any structure. Claims 4-5, 35-44, and 53 are drawn in part to (1) a genus of polynucleotides of any function wherein said polynucleotides can hybridize to the polynucleotides of SEQ ID NO: 1 or 41 under the conditions recited and comprise a region which is completely complementary to a fragment of a mammalian methionine synthase reductase nucleic acid as interpreted above, or (2) a genus of polynucleotides of any function wherein said polynucleotides are structural homologs of the polynucleotide of SEQ ID NO: 1 and comprise a fragment of a mammalian synthase reductase nucleic acid as interpreted above. Claims 45-47 and 50 are drawn to the genus of polynucleotides of claims 1, 36 or 41 encoding mammalian methionine synthase reductases which (1) have a fraction of the activity of the polypeptide of SEQ ID NO: 2 as recited, (2) comprise a consensus binding site for one or more cofactors or (3) comprise the polypeptide of SEQ ID NO: 25, which is disclosed as a cofactor binding site. Claims 51-52 is directed to the genus of polynucleotides of any function of claim 4 with the added limitation that administration of said genus of polynucleotides decrease the activity of any mutant or polymorphic methionine synthase reductase. See claim interpretation in claim rejections under 35 USC 112, second paragraph.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicants were in possession of the claimed genus. In the instant case, the genera of nucleic acids claimed are large variable genera with the potentiality of encoding many different proteins (polynucleotides of any function), and/or having many distinct structures (any mammalian methionine synthase reductase).

While it is agreed that the specification discloses the human methionine synthase reductase polynucleotide of SEQ ID NO: 1, human methionine synthase reductase polynucleotides which are mutants of the polynucleotide of SEQ ID NO: 1 as set forth in SEQ ID NO: 41, 43, 45 and 47, oligonucleotides such as those disclosed in Table 1, antisense nucleic acids, and enzymatic assays to detect methionine synthase reductase activity, it is unclear as to how one of skill in the art can reasonably conclude that the information provided by the specification is sufficient to describe the variable genera of polynucleotides claimed if the specification fails to disclose (1) which are the critical structural elements required in any mammalian polynucleotide to encode a methionine synthase reductase, (2) other functions for the structural homologs of the polynucleotides of SEQ ID NO: 1 or 41 which hybridize in 2xSSC medium at 40 C as encompassed by the claims, (3) other functions for the structural homologs of the polynucleotide of SEQ ID NO: 1 as recited in the claims, (4) additional naturally-occurring methionine synthase reductase mutations or polymorphisms in other mammalian or human methionine synthase reductases addition to those described in the specification in regard to the human polynucleotide of SEQ ID NO: 1, (5) whether or not having mutations or polymorphisms not disclosed in the instant application are associated with a disease or condition, (6) the structural characteristics required in any mammalian methionine

synthase reductase such that they display only 20%-30% or 55%-75% of the activity of the polypeptide of SEQ ID NO: 2 in catalyzing the methylation of methionine synthase-cob(II)alamin, (7) the critical structural elements required in any FAD, FMN or NADPH binding site, (8) whether the polypeptide of SEQ ID NO: 25 is related to methionine synthase reductase activity, or (9) a polynucleotide which when administer to a subject results in a decrease in activity of any mutant or polymorphic methionine synthase reductase. Thus, Applicant's disclosure is deemed insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the claimed genera of polynucleotides.

In regard to those polynucleotides of any function claimed, it is noted that the enzymatic assays disclosed are related to the detection of the only function disclosed in the specification, i.e. methionine synthase reductase. Furthermore, the oligonucleotides of Table 1 or antisense polynucleotides disclosed do not provide any clue as to other functions as encompassed by the claims.

Applicant's contention that the claimed invention is adequately described due to the disclosure of SEQ ID NO: 1, 41, 43, 45, and 47 and the structural homology between one human methionine synthase reductase (SEQ ID NO: 1) and a C. elegans methionine synthase reductase is not persuasive in view of the fact that the state of the art teaches how unpredictable it is to determine function based on structural homology and how small structural changes result in major changes in function. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-

ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, as evidenced by the art, it is unclear as to how one of skill in the art can reasonably conclude that there is a great level of predictability inherent in the practice of the invention and that the disclosure of one human methionine synthase reductase and 4 mutations/polymorphisms of such reductase (i.e. the polynucleotides of SEQ ID NO: 41, 43, 45 and 47) is sufficient to adequately describe the invention.

20. Claims 1-2, 4-5, 35-47, 50-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptides of SEQ ID NO: 1, 41, 42, 43, 45 and 47, does not reasonably provide enablement for (1) any mammalian or human methionine synthase, (2) polynucleotides of <u>any function</u> wherein said polynucleotides can hybridize to the polynucleotides of SEQ ID NO: 1 or 41 under the conditions recited and further comprise a region which is completely complementary to any fragment of any mammalian methionine synthase reductase nucleic acid, wherein said fragment comprises any naturally-occurring mammalian methionine synthase reductase mutation/polymorphism, (3) polynucleotides of <u>any</u>

function wherein said polynucleotides are structural homologs of the polynucleotide of SEQ ID NO: 1 and comprise any fragment of any mammalian methionine synthase reductase nucleic acid, wherein said fragment comprises any naturally-occurring mammalian methionine synthase reductase mutation/polymorphism, (4) polynucleotides encoding mammalian methionine synthase reductases which have a fraction of the activity of the polypeptide of SEQ ID NO: 2 as recited, (5) polynucleotides encoding mammalian methionine synthase reductases which comprise any consensus binding site for FAD, FMN and NADPH, (6) polynucleotides encoding mammalian methionine synthase reductases comprising the cofactor binding site set forth in SEQ ID NO: 25, (7) the polynucleotides of any function of (2) or (3) wherein the administration of said polynucleotides decrease the activity of any mutant or polymorphic methionine synthase reductase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

21. This rejection has been applied to claims 1-2, 4-5, 35-47 by the previous Examiner of record in Paper No.11 mailed on 11 3/5/2001 and Paper No. 14, mailed on 11/16/2001. It is now applied to newly added claims 50-53 for the reasons of record and for the reasons set forth below.

22. Applicants argue that the disclosure of multiple human methionine synthase reductase nucleic acids enables one of skill in the art to determine the sequence of any other human methionine synthase reductase nucleic acid and submit that one could use the oligonucleotide primers of Table 1 or any other primer to isolate such nucleic acids. In addition, Applicants argue that one of skill in the art can use other molecular biology techniques to clone a

representative number of mammalian methionine synthase reductase genes and mutate the polynucleotides of SEQ ID NO: 1, 41, 43, 45 and 47 or other polynucleotides isolated using such techniques. Furthermore, it is Applicant's contention that the enzymatic assays disclosed would allow for testing of the polypeptides encoded by the polynucleotides isolated as indicated above. Applicants also submit that the claimed polynucleotides have numerous uses that do not required the encoded polypeptide to have enzymatic activity such as in diagnostic methods to detect mutations or polymorphisms associated with altered risk for a disease, as PCR primers, as probes to detect mutant methionine synthase reductase genes. It is Applicant's contention that these diagnostic methods are dependent on the properties of the claimed polynucleotides and not on the properties of the encoded polypeptides. In regard to therapeutic uses, Applicants assert that the claimed polynucleotides can be used to decrease the activity of a mutant methionine synthase reductase in a patient.

23. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection in regard to claims 1-2, 4-5, 35-47 or to avoid the rejection of newly added claims 50-53. The scope of the claims, as already described above, is not commensurate with the enablement provided in regard to the large number of unknown mammalian synthase reductase polynucleotides, mutations, polymorphisms, as well as the extremely large number of polynucleotides of unknown functions encompassed by the claims. While it is agreed that one of skill in the art can use (1) well-known molecular biology techniques to isolate polynucleotides and create mutations, (2) use the oligonucleotides of Table 1 to isolate other polynucleotides, and (3) use the enzymatic assay to test for methionine synthase reductase activity, the Examiner disagrees with Applicant's contention that the full scope of the claimed invention is enabled for

the following reasons. As indicated above, determining the function of nucleic acids based solely on structural homology is unpredictable. See the teachings of Bork, Broun et al., Van de Loo et al., Seffernick et al., and Witkowski et al. already discussed. As such, while isolating/making the claimed polynucleotides can be achieved using the teachings of the art in regard to molecular biology techniques, determining the. functional characteristics of such polynucleotides and how to use them constitute undue experimentation. In addition, while testing a limited number of nucleic acids to determine if they encode a methionine synthase reductase or a methionine synthase reductase with the functional characteristics recited in the claim (i.e. 20%-30% or 55%-75% of the activity of the polypeptide of SEQ ID NO: 2) may not be considered undue experimentation, testing an infinite number of nucleic acid structural homologs of the polynucleotide of SEQ ID NO: 1, 41, 43, 45 or 47, including those containing an infinite number of mutations and/or polymorphisms, as encompassed by the claims, would constitute undue experimentation in the absence of any teaching or guidance as to which structural elements are potentially required to encode polypeptides with the desired characteristics. Furthermore, while the claimed invention encompasses any naturally-occurring mutations and/or polymorphisms in any mammalian methionine synthase reductase gene, the specification provides no clue as to the structural characteristics which are characteristic of any naturally-occurring mutation or polymorphisms in any mammalian methionine synthase reductase gene.

In regard to other uses for the claimed polynucleotides which do not require knowledge of the function of the polypeptide encoded such as in diagnostics, it is noted that such uses would have to be specific and substantial or well-established and in addition, they would have to be

enabled by the specification. In the instant case, it is unclear as to how the full scope of the claimed nucleic acids is enabled for diagnostic use such as to detect mutations or polymorphisms associated with a disease or condition if only two polymorphisms (Example VI) and two mutations (Example V) in a single human methionine synthase reductase nucleic acid (SEQ ID NO: 1) have been found which may be associated with a greater risk for neural tube defects. In regard to cancer or cardiovascular disease, it is noted that the specification, while merely stating a potential correlation with cancer and cardiovascular diseases, does not provide any experimental evidence which show a correlation between the two mutations or the two polymorphisms disclosed and these diseases. As indicated above, there is no information as to other naturally-occurring mutations or polymorphisms in other mammalian methionine synthase reductases, including additional human mutations/polymorphisms, nor there is any information as to other conditions associated with other mutations/polymorphisms. In addition, there is no disclosure of a single nucleic acid such that when administered to a subject resulted in reduced activity of any mutant methionine synthase reductase, nor there is disclosure of all the mutant methionine synthase reductases which are associated with some harmful condition such that the administration of such nucleic acid is desirable. Therefore, in view of the teachings of the specification, the lack of relevant examples, the state of the art in regard to assigning function based on structural homology, one of skill in the art would have to go through the burden of undue experimentation in order to practice the full scope of the claimed invention.

Allowable Subject Matter

24. Claim 3 appears to be allowable over the prior art of record but it is objected to since it depends upon a rejected claim.

Conclusion

25. No claim is in condition for allowance.

26. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

27. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
August 1, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
1600